1fr 1624



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|---|
| In re Application of | ) | |
| | ) | |
| Wang, *et al.* | ) | Art Unit: 1624 |
| | ) | |
| Application No. 10/534,602 | ) | Examiner: Mark L. Berch |
| | ) | |
| Filing Date: June 13, 2005 | ) | Confirmation No. 8485 |
| | ) | |
| For: NEW CRYSTAL FORM OF ADEFOVIR DIPIVOXIL AND ITS COMPOSITION | ) | |

## COMMUNICATION

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NEEDLE & ROSENBERG, P.C.
Customer Number 23859

February 27, 2008

Sir:

This communication is to respectfully request that the following enclosed documents be placed with the other papers in the file of the above-referenced application:

1. Certified Copy of priority document, Chinese Patent Application No. 02148923.8, filed November 12, 2002.

2. Verified English translation of Chinese Patent Application No. 02148923.8, filed November 12, 2002.

No fee is believed to be due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.Respectfully submitted,

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**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8**

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February 27, 2008
Date

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# 证　　明

本证明之附件是向本局提交的下列专利申请副本

请　　日：　2002.11.12

请　　号：　02148923.8

请 类 别：　发明专利

创造名称：　包含晶状埃地双酯的药用组合物

请　　人：　天津市金士力药物研究开发有限公司

或设计人：　王国成、吕新波、刘钦宣、汤宇、杨丽萍

中华人民共和国
国家知识产权局局长　田力普

2007 年 12 月 19 日

# 权 利 要 求 书

1. 一种包含治疗有效量的晶状埃地双酯和可药用载体的药物组合物。

2. 如权利要求 1 的组合物，其特征在于其结晶的 DSC 图在约 94.5℃有吸热峰。

3. 如权利要求 1 的组合物，其特征在于其结晶熔点为 90℃—95℃。

4. 如权利要求 1 的组合物，其特征在于其结晶粉末 X-射线衍射图中使用 Cu 靶辐射，以度 2θ 表示的特征峰通常在约 3.60 和/或约 7.28 和/或约 15.08 和/或约 17.24 和/或约 17.96 和/或约 20.12 和/或约 22.24 有峰。

5. 如权利要求 1 的组合物，其特征在于其结晶的傅立叶红外光谱图通常在 3320 $cm^{-1}$，约 3160 $cm^{-1}$，约 2975 $cm^{-1}$，，约 1755 $cm^{-1}$，约 1650 $cm^{-1}$处有峰。

6. 如权利要求 1 的组合物，其特征在于所述埃地双酯包含至少 70%的晶状埃地双酯。

7. 如权利要求 1-4 之一的组合物，其特征在于为片剂或胶囊剂形式。

8. 如权利要求 7 的组合物，其特征在于埃地双酯的含量为 100- 400mg/剂量单位。

9. 如权利要求 7 的组合物，其特征在于埃地双酯的含量为 1-80 mg/剂量单位。

10. 一种制备权利要求 1 中所述晶状埃地双酯的方法，其特征在于将含 98.0 %以上的埃地双酯进行喷雾干燥。

11. 如权利要求 10 的方法，其特征在于溶剂为乙醇。

12. 如权利要求 10 的方法，其特征在于喷雾干燥的进样口温度为 60℃—120℃。

# 说　明　书

## 包含晶状埃地双酯的药用组合物

本发明涉及包含核苷酸类似物的组合物，具体地说，是涉及含有结晶形态的9-[2-[双(新戊酰氧基)甲氧基]氧膦基]甲氧基]乙基]腺嘌呤的药用组合物。本发明还涉及这些组合物和结晶的制备方法。

新一代的抗病毒药物埃地双酯，即9-[2-[双(新戊酰氧基)甲氧基]氧膦基]甲氧基]乙基]腺嘌呤(adefovir dipivoxil，以下简称"AD")，是一种核苷酸逆转录酶抑制剂，在人体内对HIV和乙肝病毒均有抑制作用。有关AD抗病毒活性的描述，可参见Barditch-Crovo P等，*J Infect Dis*, 176(2):406，1997年；Starrett等，*J Med Chem*, 37:1857-1864，1994年。

在现有技术中，AD可以无定形或结晶形式提供。WO0035460A描述了含有碱性赋形剂的更为稳定的AD药物制剂，其中包括AD无水结晶和AD二水结晶。WO9904774A描述了含有一种或多种晶状AD的组合物，其中AD包括具有不同熔点的几种晶状：(无水)结晶形、水合形、溶剂化形、盐结晶形。本领域技术人员熟知，结晶药物的不同晶型具有不同的熔点、溶解度和密度，同时，结晶颗粒的流动性、弹性变形性以及制剂的溶出速率、稳定性和有效性等方面均可能存在不同程度的差异，例如吲哚拉新，其γ型稳定性差，但溶解性、生物利用度和药效方面均好于α和β型。另外，不同的晶型在一定条件下会相互转换，例如在湿法制粒中使用溶剂可使少量药物溶解而在干燥过程中重结晶形成新的结晶，这对药物的溶出和制剂的均匀性都可能有影响，因此应选择其具有适宜加工稳定性和贮存稳定性的晶型。以胰岛素锌为例，稳定型的溶解慢，亚稳定型溶解快，通过调节两者的比例可长、中或速效的混悬液制剂。因此，在制药工业中不一定采用最稳定的晶型，这要根据临床需求和生产的成本、周期及工艺等因素来确定。

本发明人惊奇地发现，将常规方法合成的AD经喷雾干燥后，可制得具有适宜熔点和稳定性的结晶AD。经DSC、IR、粉末X-Ray、熔点分析表明，本发明结晶是一种明显不同于现有晶状AD的无水结晶AD，其结晶的DSC图在约94.5

℃有吸热峰（见图1）；熔点为90℃—95℃；其结晶粉末X-射线衍射图（见图2，数据附后）中以度2θ表示的特征峰通常在约3.60，约7.28，约7.76，约12.32，约15.08，约16.28，约17.24，约17.96，约20.12，约21.40，约22.24有峰，典型图通常在约3.60和/或约7.28和/或约15.08和/或约17.24和/或约17.96和/或约20.12和/或约22.24有峰；其结晶的傅立叶红外光谱图（见图3）为通常在约3320 $cm^{-1}$，约3160 $cm^{-1}$，约2975 $cm^{-1}$，约2935 $cm^{-1}$，约1755 $cm^{-1}$，约1650 $cm^{-1}$，约1595 $cm^{-1}$，约1385 $cm^{-1}$，约1355 $cm^{-1}$，约1152$cm^{-1}$处有峰，其典型图谱通常在3320 $cm^{-1}$，约3160 $cm^{-1}$，约2975 $cm^{-1}$，，约1755 $cm^{-1}$，约1650 $cm^{-1}$处有峰；其结晶放大的照片见图4。经HPLC分析表明，该晶状AD的纯度至少为98％，优选为99.0-99.8%。本发明晶状AD在10-25℃，相对湿度50％下的空气中放置3个月后，其晶格结构稳定，且在相同条件下重现性好，满足制备临床使用的AD制剂的需要。

本发明的一个目的是提供一种药物组合物，其中包含治疗有效量的稳定晶状 AD 和可药用的载体或稀释剂。本发明药物组合物可经任何适于给药的途径方便地施用，例如，可经口服、局部、非肠道或吸入，优选经口服施用。通常，采用标准的制药技术，即可将晶状 AD 和常规药用载体制得本发明药物组合物。这些方法包括混合、制粒和压制。本领域技术人员熟知，可药用载体或稀释剂的形式和特性取决于与其混合的活性成分的量、给药途径和其他已知因素。以组合物总重量计中，活性物质 AD 的用量约为 1-40%，优选用量为 5-30%重量。所用的 AD 包含至少 70％的晶状 AD。可以理解的是，本发明药物组合物也可任选包含一定量的无定形 AD，这对于改善该组合物的生物利用度和药效可能是有益的。

本发明的另一个目的是对现有制备方法加以改良，提供一种制备晶状AD的方法。喷雾干燥是一种常规的制药技术，药物经喷雾干燥处理后其晶型很可能因溶剂、温度和干燥速度等条件的不同而出现变化，其成品的晶型是无法预测的。本发明晶状AD是采用有机溶剂喷雾干燥制得的，优选为乙醇。以乙醇为溶剂，一方面是由于其毒性很低，有机溶剂残留低。另一方面是由于AD在乙醇中溶解度大，且乙醇宜于挥发，在制备过程中乙醇用量相对于其他溶剂来说很小。在进行喷雾干燥时，进样口温度适宜控制在60-120℃，优选

为70-100℃，是有利的。本发明方法制得的晶状AD的是一种亚稳定型结晶(熔点约为94.5℃)，因此，也可任选地在喷雾过程中加入适宜的辅料，以防止其发生晶型转变的可能性。所述适宜辅料例如PVP、羧甲基纤维素钠、微粉硅胶等。本发明喷雾干燥所制得的药物粒子具有良好的溶解性、分散性和流动性。本发明方法的重现性好，适合于大规模生产结晶AD。

本发明的另一个目的是提供包含晶状AD的剂型。AD具有较高的亲脂性，口服后易于吸收，并可在体内迅速水解生成其母体化合物PMEA。目前，含有AD的制剂主要是溶液剂和片剂与胶囊剂。已有的研究表明，AD水混悬液的PMEA口服生物利用度不受药物溶解率的影响，因此AD的最适宜剂型应为胶囊或片剂。可将所述药物与适当的药用载体混合后，压制成固体剂量单位例如丸剂、片剂，或者加工成胶囊剂。在剂量单位例如片剂的制造中，可以考虑采用常规添加剂例如填充剂、着色剂、粘合剂等。通常，本发明剂型中晶状AD的含量在治疗爱滋病抗病毒剂量约为100 -400 mg/剂量单位，优选为100- 200mg/剂量单位，本发明剂型中晶状AD的含量在治疗乙肝等抗病毒剂量约为1 -80 mg/剂量单位，优选为5-20mg/剂量单位。

在此所用的药用载体是可与组合物联用给药的各种有机或无机载体，例如：用于固体制剂的赋形剂、润滑剂、粘合剂和崩解剂；也可使用药用添加剂例如着色剂和甜味剂。

优选的示例赋形剂包括：乳糖、糖、D-甘露醇、D-山梨醇、淀粉、α-淀粉、糊精、结晶纤维素、低取代的羟丙基纤维素、羧甲基纤维素钠、阿拉伯胶、糊精、支链淀粉、轻质无水硅酸、合成硅酸铝、硅酸铝镁等。

优选的示例润滑剂包括：硬脂酸镁、硬脂酸钙、滑石粉、硅胶等。

优选的示例粘合剂包括：α-淀粉、蔗糖、明胶、阿拉伯胶、甲基纤维素、羧甲基纤维素、羧甲基纤维素钠、结晶纤维素、糖、D-甘露醇、海藻糖、糊精、支链淀粉、羟丙基纤维素、羟丙基甲基纤维素、吡咯烷酮等。

优选的示例崩解剂包括：乳糖、糖、淀粉、羧甲基纤维素、羧甲基纤维素钙、氨烷基钠、羧甲基淀粉钠、轻质无水硅酸、低取代的羟丙基纤维素等。

优选的示例着色剂包括：水溶性食用枸橼黄(tar)染料(食用染料例如食

用红No. 2和No. 3，食用黄No. 4和No. 5，食用蓝No. 1和No. 2)；水不溶性色沉染料(例如上述水溶性食用枸橼黄染料的铝盐)；天然染料(例如β-胡萝卜素、叶绿素、铁丹)等。

优选的示例甜味剂包括：糖精钠、甘草次酸二钾、阿司帕坦、甜菊等。

以下实施例旨在进一步说明本发明，并不对本发明的范围加以限制。

## 实施例1　制备晶状AD

按*J Med Chem*, 37: 1857-1864，1994年Starrett等描述的代表性方法制备AD，其公开内容引入作为参考。然后采用乙腈/二正丁基醚重结晶得到纯度为99.2%的AD。最后进行喷雾干燥，得晶状AD。经HPLC分析，纯度为99.2%。

## 实施例2　制备晶状AD

按*J Med Chem*, 37: 1857-1864，1994年Starrett等描述的代表性方法制备AD，其公开内容引入作为参考。然后采用丙酮/二正丁基醚重结晶得到纯度为99.0%的AD。最后进行喷雾干燥，得晶状AD。经HPLC分析，纯度为99.0%。

## 实施例3　表征晶状AD

图1为此晶状AD的DSC图，我们采用NETZSCH DSC分析仪，样品量3.206mg，升温速率：10℃/min，结果为其结晶的TG-DTA图在约94.5℃有吸热峰；图2为此晶状AD的粉末X-射线衍射图，其数据附后，采用日本理学D/max2500型衍射仪，采用Cu靶40kv100mA扫描2θ，结果为以度2θ表示的特征峰通常在约3.50和/或约7.28和/或约15.08和/或约17.20和/或约17.92和/或约20.08和/或约22.20有峰；图3为此晶状的傅立叶红外光谱图，采用Nicolet Magna-560型红外光谱仪，KBr压片，结果为通常在3320 $cm^{-1}$，约3160 $cm^{-1}$，约2975 $cm^{-1}$，，约1755 $cm^{-1}$，约1650 $cm^{-1}$处有峰；其结晶放大的照片见图4。

## 实施例4　制备包含晶状AD的片剂

按下述处方将实施例1制得的晶状AD配制成每片含10mg AD的片剂。

处方表：

| | |
|---|---|
| 结晶AD | 10mg |
| 乳糖 | 65mg |
| 预胶化淀粉 | 25mg |
| 交联羧甲基纤维素钠 | 3mg |
| 微粉硅胶 | 0.25mg |
| 硬脂酸镁 | 0.30mg |

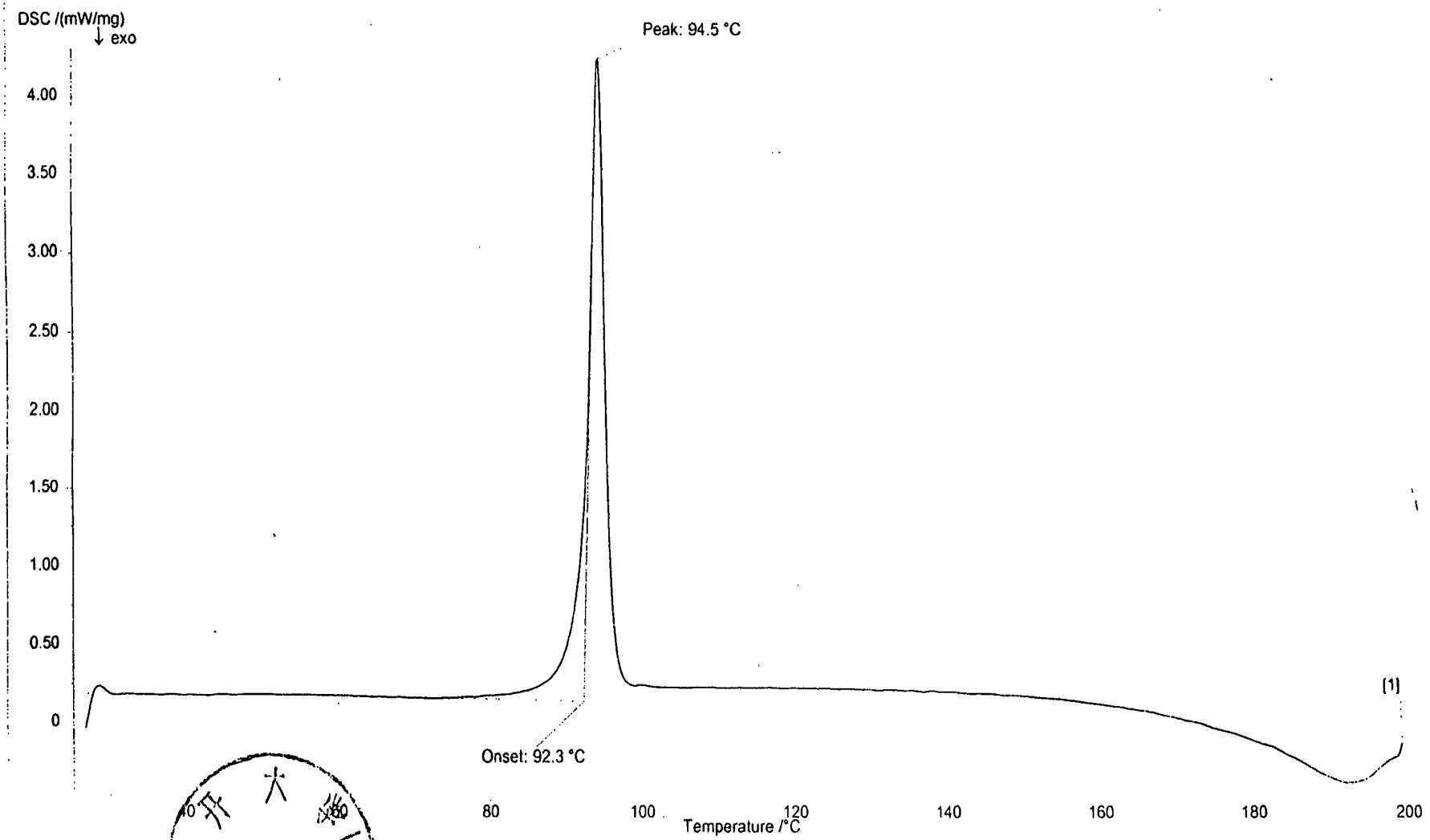
将结晶AD、乳糖、预胶化淀粉、交联羧甲基纤维素钠分别过65目筛备用。按处方量称量阿德福韦酯，按等量递加法与其他辅料混合均匀，过65目筛3次；测休止角，小于30°；测含量，定片重；将该粉末用6.5mm平斜冲头直接压片。

## 实施例5　制备包含晶状AD的胶囊剂

按下述处方将实施例1制得的晶状AD配制成每个胶囊含10mg AD的片剂。处方表:

| | |
|---|---|
| 结晶AD | 10mg |
| 乳糖 | 135mg |
| 预胶化淀粉 | 25mg |
| 交联羧甲基纤维素钠 | 3mg |
| 微粉硅胶 | 0.25mg |
| 硬脂酸镁 | 0.30mg |

将结晶AD、乳糖、预胶化淀粉、交联羧甲基纤维素钠分别过65目筛备用。按处方量称量阿德福韦酯，按等量递加法与其他辅料混合均匀，过65目筛3次；测休止角，小于30°；测含量，定装量；将该粉末装3号胶囊。




| | | | | | |
|---|---|---|---|---|---|
| Instrument: | NETZSCH DSC 204 | Sample: | AD-1, 3.206 mg | Mode/Type of Meas.: | DSC / Sample |
| File: | lianhli12.sdc | Reference: | | Segments: | 1/1 |
| Project: | temperature calibration | Material: | Empty | Crucible: | Pan Al, pierced lid |
| Identity: | lianhli | Corr./Temp.Cal: | / 20021105.tdd | Atmosphere: | ---/--- / N2/22 |
| Date/Time: | 11/8/2002 2:51:51 PM | Sens.File: | 20021105.edd | Corr/M.Range: | 000/500 uV |
| Laboratory: | State Key Laboratory | Range: | 25 °C/10.0(K/min)/200 °C | Remark: | |
| Operator: | Li Yanhong | Sample Car./TC: | DSC 204 I-sensor / E | | |

图 1

# Peak search

| | | | | | |
|---|---|---|---|---|---|
| Sample | : AD | [Smoothing ] | mode : Savitzkey-Golay's | Points | : 9 |
| File | : g.5244 | [B.G. elimination ] | | | |
| Comment | : Cu40KV100mA | | | | |
| Date | : 08-Nov-02 15:33 | [Ka2 elimination ] | | | |
| Operator | : rigakudmax | [Peak search ] | | Typical width | : 0.20 |
| | | | | Minimum height | : 100.000 |

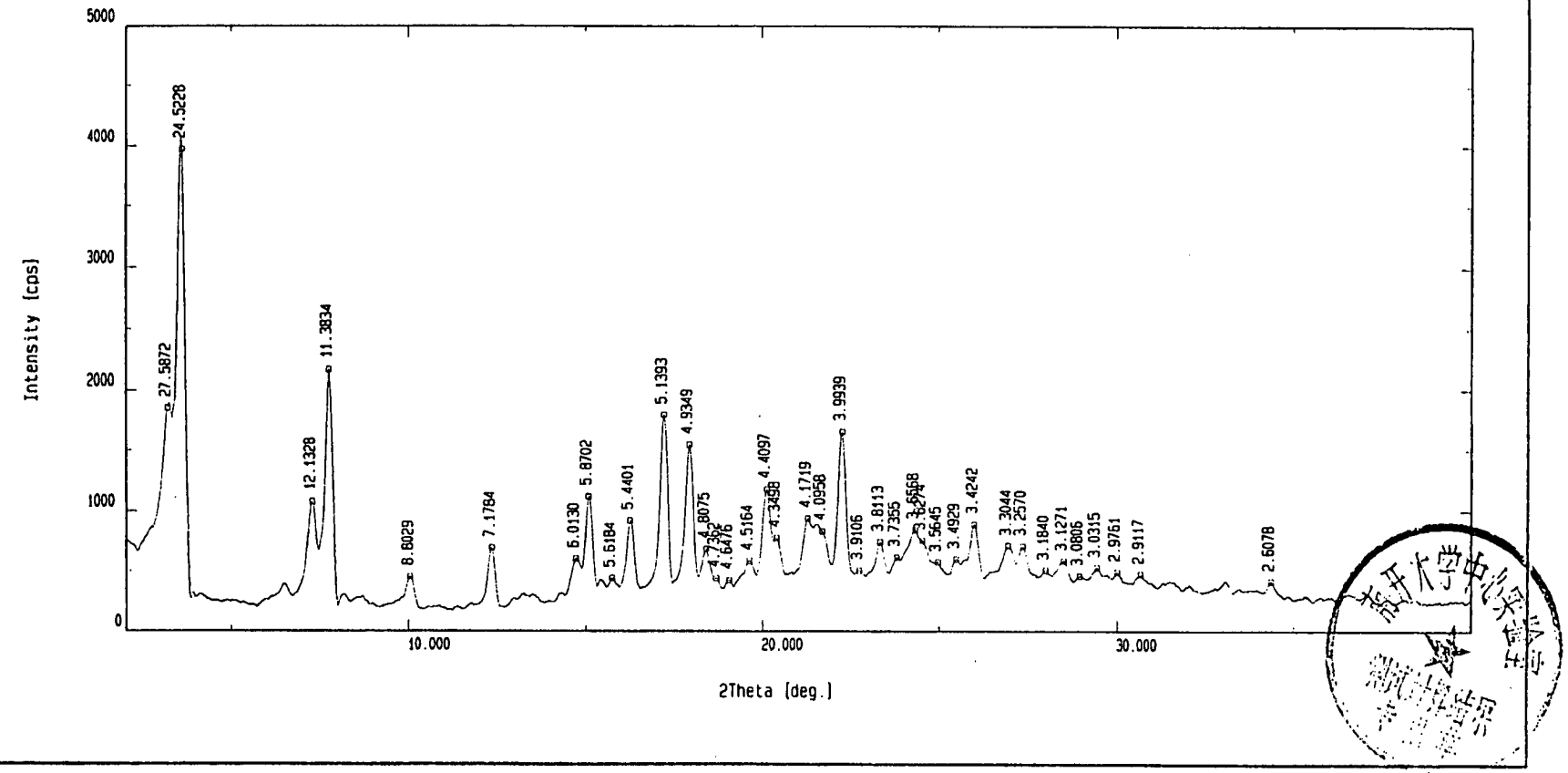





図 2

## Peak search

Sample : AD
Date : 08-Nov-02 15:33
File : g.5244
Operator : rigakudmax
Comment : Cu40KV100mA

| Peak No. | 2Theta | FWHM | d-value | Intensity | I/Io | Peak No. | 2Theta | FWHM | d-value | Intensity | I/Io |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.200 | 0.188 | 27.5872 | 1854 | 47 | 31 | 27.360 | 0.235 | 3.2570 | 712 | 18 |
| 2 | 3.600 | 0.235 | 24.5228 | 3976 | 100 | 32 | 28.000 | 0.188 | 3.1840 | 509 | 13 |
| 3 | 7.280 | 0.235 | 12.1328 | 1078 | 27 | 33 | 28.520 | 0.282 | 3.1271 | 587 | 15 |
| 4 | 7.760 | 0.235 | 11.3834 | 2172 | 55 | 34 | 28.960 | 0.235 | 3.0806 | 463 | 12 |
| 5 | 10.040 | 0.235 | 8.8029 | 456 | 11 | 35 | 29.440 | 0.235 | 3.0315 | 531 | 13 |
| 6 | 12.320 | 0.235 | 7.1784 | 694 | 17 | 36 | 30.000 | 0.188 | 2.9761 | 497 | 12 |
| 7 | 14.720 | 0.235 | 6.0130 | 602 | 15 | 37 | 30.680 | 0.282 | 2.9117 | 478 | 12 |
| 8 | 15.080 | 0.282 | 5.8702 | 1118 | 28 | 38 | 34.360 | ***** | 2.6076 | 422 | 11 |
| 9 | 15.760 | 0.141 | 5.6184 | 442 | 11 | | | | | | |
| 10 | 16.280 | 0.282 | 5.4401 | 922 | 23 | | | | | | |
| 11 | 17.240 | 0.235 | 5.1393 | 1795 | 45 | | | | | | |
| 12 | 17.960 | 0.235 | 4.9349 | 1543 | 39 | | | | | | |
| 13 | 18.440 | 0.235 | 4.8075 | 686 | 17 | | | | | | |
| 14 | 18.720 | 0.141 | 4.7362 | 442 | 11 | | | | | | |
| 15 | 19.080 | 0.188 | 4.6476 | 427 | 11 | | | | | | |
| 16 | 19.640 | 0.235 | 4.5164 | 585 | 15 | | | | | | |
| 17 | 20.120 | 0.282 | 4.4097 | 1176 | 30 | | | | | | |
| 18 | 20.400 | 0.141 | 4.3498 | 778 | 20 | | | | | | |
| 19 | 21.280 | 0.188 | 4.1719 | 938 | 24 | | | | | | |
| 20 | 21.680 | 0.376 | 4.0958 | 835 | 21 | | | | | | |
| 21 | 22.240 | 0.282 | 3.9939 | 1652 | 42 | | | | | | |
| 22 | 22.720 | 0.235 | 3.9106 | 507 | 13 | | | | | | |
| 23 | 23.320 | 0.235 | 3.8113 | 744 | 19 | | | | | | |
| 24 | 23.800 | 0.235 | 3.7355 | 617 | 16 | | | | | | |
| 25 | 24.320 | 0.188 | 3.6568 | 850 | 21 | | | | | | |
| 26 | 24.520 | 0.188 | 3.6274 | 758 | 19 | | | | | | |
| 27 | 24.960 | 0.141 | 3.5645 | 577 | 15 | | | | | | |
| 28 | 25.480 | 0.188 | 3.4929 | 604 | 15 | | | | | | |
| 29 | 26.000 | 0.235 | 3.4242 | 893 | 22 | | | | | | |
| 30 | 26.960 | 0.329 | 3.3044 | 714 | 18 | | | | | | |



图 2 数据

Best Available Copy

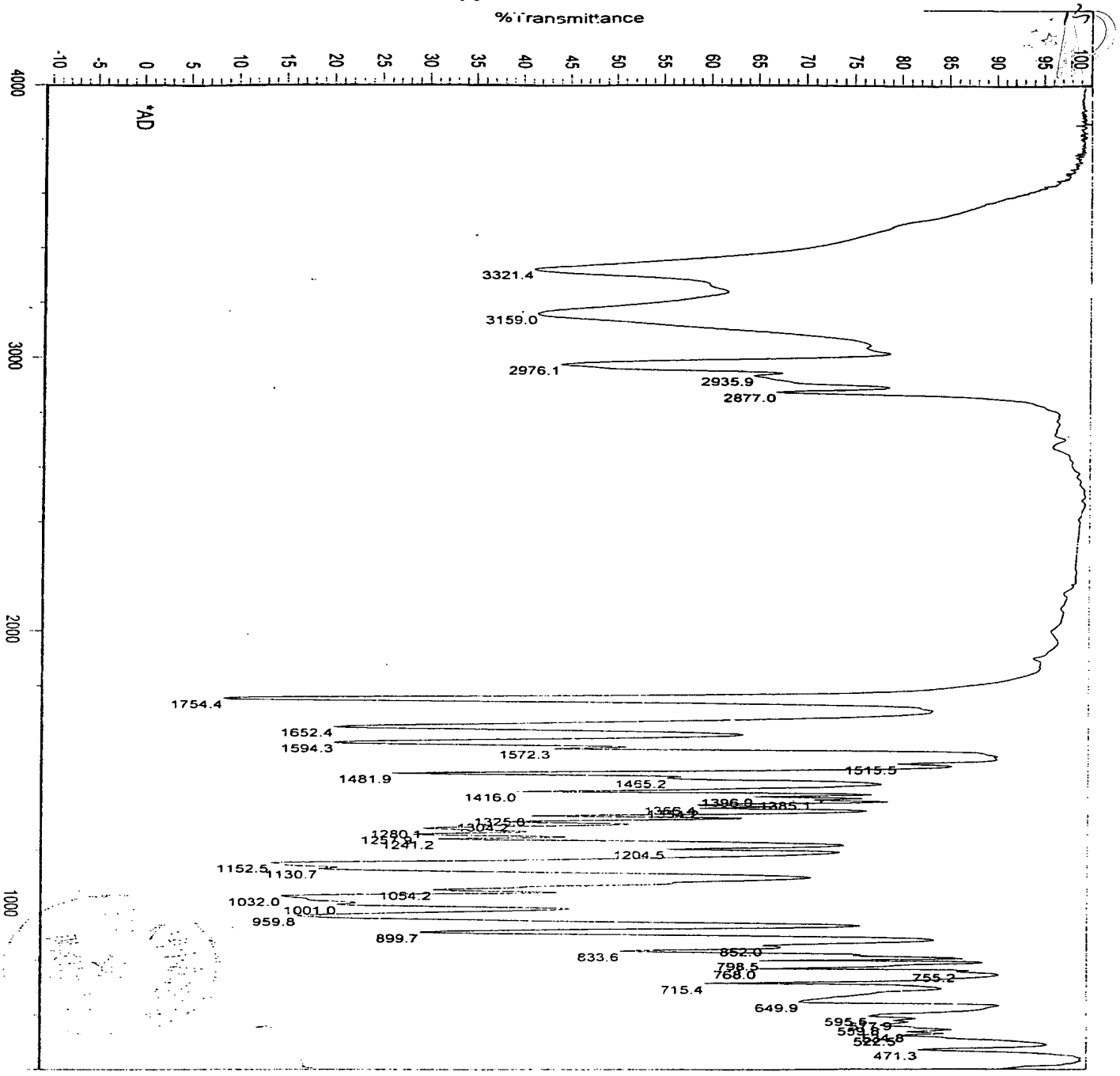



图 3

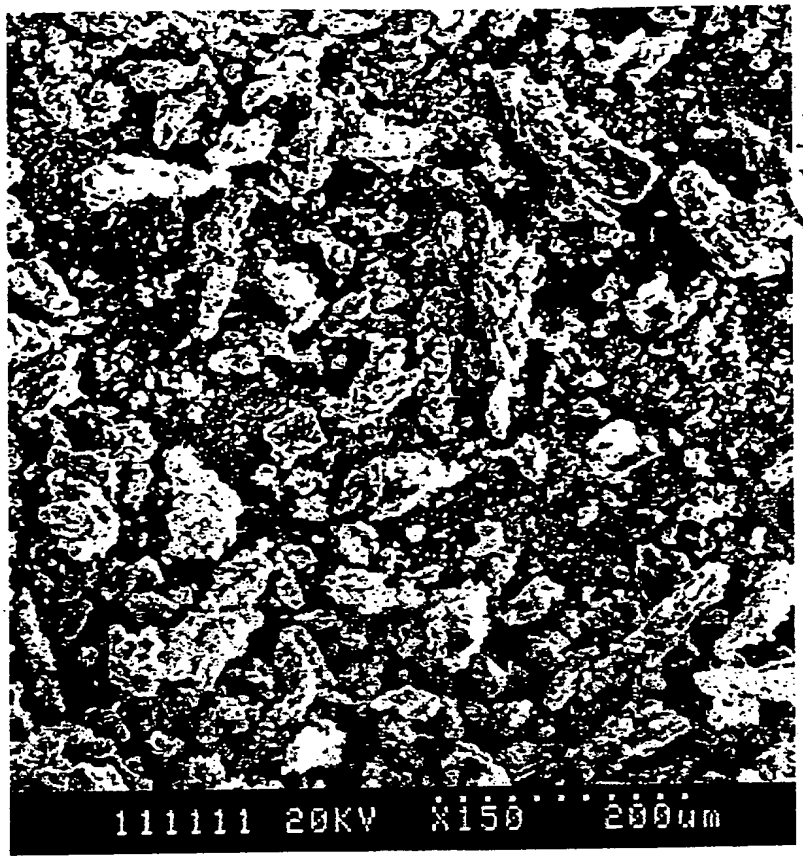




图 4

**VERIFICATION OF TRANSLATION**

I, ZHANG Guangyu

of Peksung Intellectual Property Ltd.
do hereby certify that I am familiar with the English and Chinese languages and that to the best of my knowledge and belief the following is a true translation into the English language of the specification of CN 02148923.8 published in Chinese.

Dated this 2nd day of February 2, 2008.

Signature of translator:

ZHANG Guangyu

State Intellectual Property Office of the People's Republic of China

# CERTIFICATE

This is to certify that the attachment is a copy of the following patent application filed with this Office.

| | |
|---|---|
| Filing Date: | November 12, 2002 |
| Application Number: | 02148923.8 |
| Type of the Application: | Invention Patent |
| Title of the Invention Creation: | A Pharmaceutical Composition Containing Crystalline Adefovir Dipivoxil |
| Applicant: | Tianjin Kinsly Pharmaceutical Co. Ltd. |
| Inventors or Designers: | WANG Guocheng, LU Xinbo, LIU Qinxuan, TANG Yu, YANG Liping |

**TIAN Lipu**
the Commissioner
on December 19, 2007

# A Pharmaceutical Composition Containing Crystalline Adefovir Dipivoxil

## Field of the invention

The present invention relates to a composition containing nucleotide analog, more specially, it relates to a pharmaceutical composition containing crystalline 9-[2-[bis(pivaloyloxy)-methoxy]phosphinyl]methoxy)ethyl] adenine. The present invention also discloses a process for preparing this new crystalline form.

## Background of the invention

The new antiviral drug, adefovir dipivoxil (hereinafter "AD"), is a nucleotide reverse transcriptase inhibitor with the nomenclature of 9-[2-[bis(pivaloyloxy)-methoxy]phosphinyl]methoxy)ethyl] adenine, which exhibits a marked *in vivo* antiviral activity against both HIV and HBV. For more information about its antiviral activities, see Barditch-Crovo P et al, J Infect Dis, 176(2): 406,1997, and Starrett et al,J Med Chem, 37:1857-1864,1994.

According to the prior art, AD may be provided in two forms: amorphism and crystal. PCT patent application "pharmaceutical formulations" (International Publication NO. WO0035460A) discloses a more stable AD pharmaceutical formulations comprising anhydrous crystalline AD and dihydrate crystalline AD and an alkaline excipient. Another application, WO9904774A, discloses compositions containing one or more crystalline AD, wherein the AD comprises the following crystalline forms with different melting points: the anhydrous crystalline form, the hydrated form, the solvate form, and the salt crystalline form. It is well known that different crystalline forms of a drug compound have different melting points, solubility, and density of said drug compound. At the same time, the fluidity and flexibility of crystals of said compound and the dissolution rate, stability, and effectiveness of said crystals in a pharmaceutical formulation may differ from one to another. For example, although the γ-type of indolacin is less stable, it has better performance in solubility, bioavailability and pharmacology than that of the α and β type. In addition, different crystalline

forms may be enantiotropic under certain conditions. For instance, during the process of wet granulation, the drug may be dissolved in a solvent added and recrystallized in the later drying step to obtain a new crystalline form, which may affect the dissolution of the drug and the uniformity of the pharmaceutical formulation containing this drug. Therefore it is necessary to select a crystalline form with a suitable stability during manufacture and storage. Taking insulin zinc as an example, the dissolution rate of its stable form is slower than that of its metastable one. Thus a suspension of short, medium or long term release may be obtained by adjusting the proportion of these two crystalline forms. Therefore, it is not always necessary to adopt the most stable crystalline form in pharmaceutical industry, which depends on a lot of factors, such as the clinical uses, producing costs and cycles, as well as techniques and so on.

**Contents of the invention**

When carrying out studies on the AD, the inventor of this invention surprisingly discovered that a conventionally synthesized AD can be prepared into a novel crystalline form of AD having good stability and a proper melting point through dry spraying. Further, by differential scanning calorimetry (DSC), infrared absorption spectrum (IR), powder X-Ray diffraction (XRD), melting point measurement, this crystalline AD is identified as an anhydrous crystal which is substantially different from those already-existing ones in that: its endothermic peak in DSC thermogram is about 94.5 ℃ (see Figure 1); its melting point is 94 ℃-95 ℃; its XRD pattern (see Figure 2) usually shows a characteristic peak(s) expressed in terms of $2\theta$ at about 3.60, and/or about 7.28, and/or about 7.76, and/or about 12.32, and/or about 15.08, and /or about 16.28, and/or about 17.24, and/or about 17.96, and/or about 20.12, and/or about 21.40, and/or about 22.24, and more typical peak(s) at about 3.60, and/or about 7.28, and/or about 15.08, and/or about 17.24, and/or about 17.96, and/or about 20.12, and/or about 22.24, its Fourier Transform Infrared Spectrum (FTIR) (see Figure 3) shows a peak(s) at about 3320 $cm^{-1}$, about 3160 $cm^{-1}$, about 2975 $cm^{-1}$, about 2935 $cm^{-1}$, about 1755 $cm^{-1}$, about 1650 $cm^{-1}$, about 1595 $cm^{-1}$, about 1385 $cm^{-1}$, about 1355 $cm^{-1}$, and about 1152 $cm^{-1}$, and more typical peak(s) at about 3320 $cm^{-1}$, about 3160 $cm^{-1}$, about 2975 $cm^{-1}$, about 1755 $cm^{-1}$, and about 1650 $cm^{-1}$. The magnified photos of this crystalline AD are displayed

in Figure 4. By the analysis of HLPC, the purity of this crystalline AD is at least 98wt%, preferably 99.0~99.8%. The crystalline AD of this invention exhibit not only a feature of stable crystal form being exposed for a period of three months at a temperature of 10~25℃ under RH 50%, but also a good reproducibility under the same conditions, making it meet all demands of preparing the quality AD preparations fit for clinical practice.

In another aspect this invention provides a composition comprising a therapeutically effective amount of the stable crystalline AD of the invention and pharmaceutically acceptable carriers or diluents. The composition of the present invention may be administered conveniently by any routes appropriate for administration, for example the composition may be administer orally, topically, parenterally, or inhalationally, preferably administered orally. Typically, the composition of the present invention can be obtained by using the crystalline AD and conventional carriers via any of the standardized methods well known in the art. Such methods include mixing, granulating, and tableting. It is well known by one skilled in the art that the selection of forms and natures of pharmaceutically acceptable carriers or excipients depends on many factors including the amount of the active ingredients to be mixed therewith, routes of administration, and other known factors. The composition comprises as active ingredient about 1~40% of AD by weight, preferably 5~30% by weight, wherein said AD comprises at least 70% of the crystalline AD of the present invention. It is understood that the composition of the present invention may optionally comprise a given amount of the amorphous AD, which may advantageously improve both bioavailability and effectiveness of said composition.

In another aspect this invention provides a process for preparing the new AD crystal, which is an improvement of the conventional methods. The "spray drying" is a common-used pharmaceutical technique. However, after drugs are processed by spray drying, the crystalline forms thereof can vary with many factors: solvent, temperature, and drying rate etc. This will result in the uncertainty of crystalline AD in final product. The crystalline AD of this invention is prepared by spray drying via the organic solvent, preferably the ethanol, wherein ethanol is preferred due to its low toxicity,

low organic residue, high volatility and good solubility for AD, which in turn results in less consumption of ethanol during the process. During spray drying, it is helpful to control the inlet temperature properly at 60~120 ℃, preferably 70~100℃. The crystalline AD made according to this invention belongs to a metastable one with the melting point of about 94.5℃, so proper excipients may be optionally introduced into spray drying to prevent crystalline forms from transforming. Said proper excipients include PVP, Na-CMC and colloidal silicon dioxide etc. The AD particles obtained by spray drying according to the invention exhibit good dissolution, distribution, and flowability. This process has good reproducibility, suitable for the production of crystalline AD on a large scale.

In another aspect this invention provides a dosage form containing the crystalline AD. The AD is high lipophilic. It will be absorbed readily after oral administration and *in vivo* hydrolyzed to its parent compound, 9-[(phosphonomethoxy)ethyl] adenine (PMEA, adefovir) rapidly. By far, the major dosage form containing AD are solutions, tablets, and capsules. The studies have showed that in the aqueous suspensions containing AD, the bioavailability of PMEA is independent of the drug's solubility. Therefore, the suitable dosage forms of AD are tablets or capsules. The said drug may be pressed into solid unit dosage forms, such as pills, tablets or processed into capsules after being mixed with suitable pharmaceutically acceptable carriers. Conventional additives, such as fillers, colorants, and binders may be added in the preparation of unit dosage forms such as tablets. Typically, the dosage form for AIDS treatment comprises crystalline AD in an amount of 100-400 mg/unit, preferably 100 - 200 mg/unit. The dosage form for hepatitis B treatment comprises crystalline AD in an amount of 1-80mg/unit, preferably 5-20mg/unit.

According to this invention, said pharmaceutically acceptable carriers are either organic or inorganic carriers that can be administered together with active ingredients and may include the ones for solid pharmaceutical preparations, for example excipients, lubricants, binders, and disintegrants, and any pharmaceutically acceptable additives, for example colorants and sweetening agents.

The preferred excipients may be exemplified by lactose, sugar, D-mannitol, D-sorbitol, starch, α - starch, dextrine, crystalline cellulose, low-substituted hydroxypropylcellulose, sodium carboxymethylcellulose (CMC-Na), arabic gum, dextrine, amylopectin, light anhydrous silicic acid, synthesized aluminium silicate, aluminium-magnesium silicate etc.

The preferred lubricants may be exemplified by magnesium stearate, calcium stearate, talcum powders, silica gel etc.

The preferred binders may be exemplified by α -starch, sucrose, glutin, Arabic gum, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, crystalline cellulose, sugar, D-mannitol, trehalose, dextrine, amylopectin, hydroxypropylcellulose, hydroxypropylmethylcellulose(HPMC), and pyrrolidone etc.

The preferred disintegrants may be exemplified by lactose, sugar, starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl starch, light anhydrous silica acid, and low-substituted hydroxypropylcellulose.

The preferred colorants may be exemplified by water-soluble edible dyestuff citric acid yellow, for example edible red No.2, edible yellow No.4 and No.5, edible blue No.1 and No.2; water-insoluble dyestuff, for example aluminium salt of the above-mentioned edible dyestuff citric acid yellow; naturally occurring dyestuffs such as beta-carotene, chlorophyll and iron red.

The preferred sweetening agents may be exemplified by saccharin sodium, potassium glycyrrhetinate dibasic, aspartame, and stevioside.

**Examples**

The following examples further elaborate the present invention and do not by any means limit the invention.

**Example 1 Preparation of crystalline AD**

The raw AD was prepared according to the representative method as described (Starrett et al., J. Med. Chem. (1994) 37:1857-1864, hereby incorporated by reference) and was then recrystallized by acetonitrile/ dibutyl ether to obtain the AD with the purity of 99.2%. At last, spray drying was carried out to give the crystalline AD. By the analysis of HPLC, the purity amounted to 99.2%.

**Example 2 Preparation of crystalline AD**

The raw AD was prepared according to the representative method as described (Starrett et al., J. Med. Chem. (1994) 37:1857-1864, hereby incorporated by reference) and was then recrystallized by acetone/ dibutyl ether to obtain the AD with the purity of 99.0%. At last, spray drying was performed to give the crystalline AD. By the analysis of HPLC, the purity amounted to 99.0%.

**Example 3 Characterization of crystalline AD**

Figure 1 represented the DSC thermogram. Differential scanning calorimetric (DSC) experiments were carried out on a microcalorimeter (NETZSCH). 3.0206 g of sample was applied, and the heating rate was fixed at 10 ℃ per minutes. In terms of the crystalline AD prepared by foregoing method, an endothermic peak at about 94.5 ℃ was detected in DSC thermogram. Figure 2 represented powder X-ray diffraction pattern by adoption of D/max 2500 X-ray diffractometer (Rigaku Corporation, Japan). The data were enclosed. The characteristic peaks expressed in terms of 2θ at about 3.50 and/or about 7.28, and/or about 15.08, and/or about 17.20, and/or about 17.92, and/or about 20.08 and/or about 22.20 were shown in powder XRD pattern (scanning condition: Cu target, 40 kv, 100 mA). Figure 3 represented Fourier Transform Infrared Spectrum (FTIR) by means of infrared spectrum (Nicolet Magna-560). The peaks at about 3320 $cm^{-1}$, about 3160 $cm^{-1}$, about 2975 $cm^{-1}$, about 1755 $cm^{-1}$ and about 1650 $cm^{-1}$ were shown. The magnified photos of this crystalline AD were displayed in Figure 4.

**Example 4 Tablets containing the crystalline AD**

The tablets containing the crystalline AD of example 1 were prepared according to the formula as describes below, and each of the tablets contains

10 mg AD.

| Component | amount |
|---|---|
| Crystalline AD | 10 mg |
| Lactose | 65 mg |
| Pregelatinized starch | 25 mg |
| Croscarmellose Sodium | 3 mg |
| Colloidal silicon dioxide | 0.25 mg |
| Magnesium Stearate | 0.30 mg |

The crystalline AD, lactose, pregelatinized starch and croscarmellose sodium were respectively passed through 65-mesh screen for later use. The AD was weighed according to the amount as described in the formula and mixed with other adjuvants in a manner of increasing the amounts proportionally. The mixture was passed through 65-mesh screen for three times. The angle of repose was measured as less than 30° . After content tested and weight determined, tablets were prepared by direct compression of the mixture using a 6.5 mm-diameter flat punch pin.

**Example 5 Capsules containing the crystalline AD**

The capsules containing the crystalline AD of example 1 were prepared according to the formula as describes below, and each of the capsules contains 10 mg AD.

| Component | amount |
|---|---|
| Crystalline AD | 10 mg |
| Lactose | 135 mg |
| Pregelatinized starch | 25 mg |
| Croscarmellose Sodium | 3 mg |
| Colloidal silicon dioxide | 0.25 mg |
| Magnesium Stearate | 0.30 mg |

The crystalline AD, lactose, pregelatinized starch, croscarmellose sodium were respectively passed through 65-mesh screen for later use. The AD was weighed according to the amount as described in the formula and mixed

with other adjuvants in a manner of increasing the amounts proportionally. The mixture was passed through 65-mesh screen for three times. The angle of repose was measured as less than 30° . After content tested and capacity determined, capsules were prepared by loading the mixture into No.3 capsules.

**Claims**

1. A composition comprising a therapeutically effective amount of crystalline adefovir dipivoxil ( AD) and pharmaceutically acceptable carriers.

2. The composition of claim 1 characterized in that the crystalline AD has endothermic peak at about 94.5 °C in DSC thermogram.

3. The composition of claim 1 characterized in that the crystalline AD has a melting point at 90 °C~95 °C.

4. The composition of claim 1 characterized in that the crystalline AD have the characteristic peaks expressed in terms of 2θ at about 3.60, and/or about 7.28, and/or about 15.08, and /or about 17.24, and/or about 17.96, and/or about 20.12, and/or about 22.24 in X-ray powder diffraction pattern with Cu target radiation.

5. The composition of claim 1 characterized in that the crystalline AD has peaks at about 3320 $cm^{-1}$, about 3160 $cm^{-1}$, about 2975 $cm^{-1}$, about 1755 $cm^{-1}$, and about 1650 $cm^{-1}$ in Fourier Transform Infrared Spectrum.

6. The composition of claim 1 characterized in that the said AD comprises at least 70% of crystalline AD.

7. The composition of any of claim 1 to 4 characterized in that it is in the form of tablet or capsule.

8. The composition of claim 7, wherein each dosage unit contains 100-400 mg crystalline AD.

9. The composition of claim 7, wherein each dosage unit contains 1-80 mg crystalline AD.

10. A process for preparing the crystalline AD of claim 1, wherein more than 98.0% of AD is processed by spray drying.

11. The process of claim 10, wherein the organic solvent is ethanol.

12. The process of claim 10, wherein the inlet air temperature is set at 60-120 °C.

**Abstract**

The present invention discloses a pharmaceutical composition comprising a crystalline 9-[2-[bis(pivaloyloxy)-methoxy]phosphinyl]methoxy)ethyl] adenine (AD). This composition may meet all demands of preparing the AD preparations for clinical use. This invention also discloses a process of manufacturing said crystalline AD on a large scale.